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Chiral pyridinyl-oxazolines as ligands for copper(I)-catalyzed asymmetric cyclopropanation

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Abstract

New chiral ligands containing oxazoline unit and pyridine separated by a methylene group **3** have been synthesized from enantiomerically pure amino alcohols and 2-picoline using a convenient procedure. Comparative investigation of ligands **3** with chiral conjugate pyridinyl-oxazoline ligands **2** and quinolinyl-oxazoline ligands **1** in copper(I)-catalyzed asymmetric cyclopropanation of styrene with diazoacetates was described.

Keywords: Chiral ligand; Oxazoline; Asymmetric catalysis; Cyclopropanation

1. Introduction

Chiral oxazoline compounds, with and without C_2 symmetric structure, have been widely used in catalytic asymmetric synthesis [1–3]. We recently introduced nonsymmetric chiral quinolinyl-oxazolines **1** as ligands for enantioselective copper(I)-catalyzed cyclopropanation of styrene with diazoacetates obtaining good chemical yields and moderate enantiomeric excesses [4]. As a comparison, Brunner's ligands **2** [5] have also been investigated in this reaction and very poor chemical yields and enantiomeric excesses were obtained. We know that ligands **1**, upon coordination, form a six-membered chelate ring, whereas ligands **2** form a five-membered chelate ring. Is this difference in chelate ring size of catalysts a major reason for different chemical yields and enantioselectivities of these types of ligand in copper(I)-catalyzed cyclopropanation? To answer this question, chiral ligands containing oxazoline unit and pyridine separated by a methylene group **3** were synthesized and investigated in this paper. Different from ligands **2**, ligands **3** will form six-membered chelate ring upon coordination. By comparison of ligands **2** and ligands **3**, we can test

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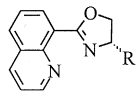
again if six-membered chelate ring in catalysts is favorable to high chemical yield and enantiomeric excess. Although both of ligands **1** and ligands **3** can form six-membered chelate rings upon coordination, heteroaryl ring and oxazoline unit are conjugated in ligands **1**, whereas they are separated by a methylene group in ligands **3**. Thus, comparative study of ligands **1** and ligands **3** should show the effect of conjugation between heteroaryl group and oxazoline unit in chemical yield and enantioselectivity in asymmetric cyclopropanation reaction.



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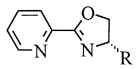

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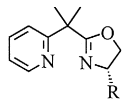

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2. Experimental

2.1. General

All reactions were carried out under an atmosphere of nitrogen. Dichloromethane and chlorobenzene were distilled from CaH_2 under argon. DMSO was distilled from CaH_2 under reduced pressure. $CHCl_3$ was distilled from $CaSO_4$ under argon. All optically pure amino alcohols were prepared by reduction of the corresponding available amino acids with $NaBH_4/I_2$ in THF [6]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ in ppm (TMS), J in Hz. IR (film): selective bands in cm^{-1}. MS (EI): selective peaks, m/z (%).

2.2. Synthesis of chiral pyridinyl-oxazoline ligands

2.2.1. 2-Methyl-2-(2-pyridinyl)propanitrile (7)

A total of 1.56 g (65 mmol) NaH was dissolved in 20 ml DMSO under N_2, a solution of 6.44 g (54 mmol) 2-cyanomethyl pyridine in 12 ml DMSO was added and stirred for 30 min, then 9.23 g (65 mmol) MeI was added dropwise at 0°C. After stirring at 0°C for 1 h, additional 1.56 g (65 mmol) NaH was added and stirred for 30 min, then additional 9.23 g (65 mmol) MeI was added dropwise at 0°C. The resulting mixture was stirred at r.t. for 9 h. Then, 60 ml ether was added, and filtered, the solid was washed with 30 ml ether. The filtrate was washed with 30 ml water and dried over anhydrous Na_2SO_4. After concentration, 4.8 g (60%) pure product was obtained by reduced distillation: 69–70°C/1 mm Hg. ^{1}H NMR ($CDCl_3$): δ 8.61 (ddd, $J = 4.8$, 1.8 and 0.9 Hz, 1H), 7.73 (dt, $J = 7.7$ and 1.8 Hz, 1H), 7.60 (dd, $J = 7.7$ and 0.7 Hz, 1H,), 7.19 (m, 1H), 1.76 (s, 6H).

2.2.2. (4S)-4,5-dihydro-2-[1-methyl-1-(2-pyridinyl)-ethyl]-4-methyl-oxazole (3a)

In a 50-ml flask, $ZnCl_2$ (1.36 g, 10 mmol) was melted under vacuum and cooled under nitrogen, then 2-methyl-2-(2-pyridinyl)propanitrile **7** (1.46 g, 10 mmol), the alaninol (825 mg, 11 mmol), and dry chlorobenzene (10 ml) was added to the flask. The mixture was refluxed for 3 days. After cooling to r.t., 10 ml saturated aqueous NH_4Cl was added to the mixture and was stirred over night. The organic phase was separated, the aqueous phase was extracted by EtOAc (5×10 ml). The organic phase was combined, and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by flash column chromatography on silica gel with petroleum ether: ethyl acetate (3:1) as eluent to give product as a white solid 1.49 g (7.3 mmol, 73%), m.p. 203–204°C, $[\alpha]_D^{20} - 68$ (c 0.23, EtOH). ^{1}H NMR ($CDCl_3$): δ 8.57 (ddd, $J = 4.9$, 1.9 and 1.0 Hz, 1H), 7.63 (ddd, $J = 8.0$, 1.9 and 1.0 Hz, 1H), 7.31 (dt, $J = 8.0$ and 1.0 Hz, 1H), 7.14 (ddd, $J = 8.0$, 4.9 and 1.0 Hz, 1H), 4.34–4.17 (m, 2H), 3.76 (dd, $J = 7.5$ and 6.9 Hz, 1H), 1.65 (s, 3H), 1.64 (s, 3H), 1.28 (d, $J = 6.9$ Hz, 3H). IR: 3100w, 2980w, 1630s, 1600s, 1480s, 1240m, 1180m, 1120m, 1030m, 960m.

MS: 204 (M^+, 9), 161 (33), 120 (100), 93 (40), 79 (28), 78 (41). HRMS ($C_{12}H_{16}N_2O$): Calcd: 204.1246; Found: 204.1254.

2.2.3. (4S)-4,5-dihydro-2-[1-methyl-1-(2-pyridinyl)-ethyl]-4-benzyl-oxazole (**3b**)

White solid, 59% yield, m.p. 194–195°C, $[\alpha]_D^{20}$ + 6.9 (c 0.29, EtOH). ^{1}H NMR ($CDCl_3$): δ 9.01 (d, J = 4.1 Hz, 1H), 8.01 (dt, J = 7.9 and 1.5 Hz, 1H), 7.61–7.57 (m, 2H), 7.29–7.25 (m, 5H), 4.90–4.85 (m, 1H), 4.43–4.39 (m, 2H), 3.34 (dd, J = 14.0 and 3.7 Hz, 1H), 3.06 (dd, J = 14.0 and 8.0 Hz, 1H), 1.79 (s, 3H), 1.75 (s, 3H). IR: 3080w, 3030w, 2990m, 2920m, 1660s, 1640s, 1480s, 1370s, 1120s, 1020s, 960s. MS: 280 (M^+, 3), 190 (13), 188 (100), 120 (67), 118 (11), 92 (11), 91 (30). HRMS ($C_{18}H_{20}N_2O$): Calcd: 280.1561; Found: 280.1568.

2.2.4. (4S)-4,5-Dihydro-2-[1-methyl-1-(2-pyridinyl)-ethyl]-4-isopropyl-oxazole (**3c**)

Colorless oil, 84% yield, $[\alpha]_D^{20}$ − 61(c 0.09, EtOH). ^{1}H NMR ($CDCl_3$): δ 8.52 (dd, J = 4.8 and 1.0 Hz, 1H), 7.62 (dt, J = 7.7 and 1.8 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.13 (ddd, J = 7.7, 4.8 and 1.0 Hz, 1H), 4.20–4.15 (m, 1H), 4.04–3.93 (m, 2H), 1.86–1.84 (m, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). IR: 3100w, 3070w, 2970w, 2880m, 1640s, 1600s, 1480m, 1400m, 1370m, 1120m, 960m, 940m. MS: 232 (M^+, 5), 190 (15), 189 (86), 163 (14), 121 (18), 120 (100), 118 (14), 92 (13), 78 (22). HRMS ($C_{14}H_{20}N_2O$): Calcd: 232.1530; Found: 232.1553.

2.2.5. (4S)-4,5-dihydro-2-[1-methyl-1-(2-pyridinyl)-ethyl]-4-phenyl-oxazole (**3d**)

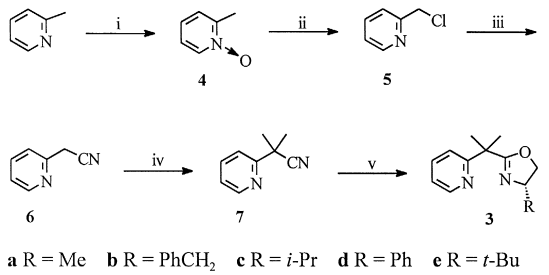
Lightly yellow oil, 41% yield. $[\alpha]_D^{20}$ − 69 (c 0.16, EtOH). ^{1}H NMR ($CDCl_3$): δ 8.60 (ddd, J = 4.8, 1.8 and 0.9 Hz, 1H), 7.65 (dt, J = 7.7 and 1.8 Hz, 1H), 7.40–7.20 (m, 6H), 7.16 (ddd, J = 7.4, 4.8 and 0.9 Hz, 1H), 5.23 (dd, J = 10.1 and 8.0 Hz, 1H), 4.59 (dd, J = 10.1 and 8.0 Hz, 1H), 4.08 (t, J = 8.0 Hz, 1H), 1.74 (s, 3H), 1.70 (s, 3H). IR: 3060w, 2940w, 1650s, 1590s, 1470s, 1250m, 1140s, 1110s, 980m. MS: 266 (M^+, 14), 253 (15), 148 (15), 147 (14), 121 (50), 120 (100), 118 (13), 92 (14). HRMS ($C_{17}H_{18}N_2O$): Calcd: 266.1301; Found: 266.1340.

2.2.6. (4S)-4,5-dihydro-2-[1-methyl-1-(2-pyridinyl)-ethyl]-4-tert-butyl-oxazole (**3e**)

Colorless oil, 77% yield, $[\alpha]_D^{20}$ − 54 (c 0.30, EtOH). ^{1}H NMR ($CDCl_3$): δ 8.56 (ddd, J = 4.8, 1.8 and 1.0 Hz, 1H), 7.62 (dt, J = 7.9 and 1.8 Hz, 1H), 7.32 (dt, J = 7.9 and 1.0 Hz, 1H), 7.13 (ddd, J = 7.9, 4.8 and 1.0 Hz, 1H), 4.10 (dd, J = 10.1 and 8.6 Hz, 1H), 4.07 (dd, J = 8.6 and 7.0 Hz, 1H), 3.89 (dd, J = 10.0 and 7.0 Hz, 1H), 1.65 (s, 6H), 0.91 (s, 9H). IR: 3070w, 3000w, 2970m, 2860m, 1630s, 1600s, 1480s, 1370s, 1230s, 1110s, 1020m, 950m. MS: 248 (M^+ + 2, 100), 190 (10), 189 (73), 120 (100), 57 (12). HRMS ($C_{15}H_{22}N_2O$): Calcd: 246.1716; Found: 246.1724.

2.3. Copper(I)-catalyzed asymmetric cyclopropanation of styrene with diazoacetates

General procedure: to a suspension of 5.0 mg (0.02 mmol) of $CuOTf(C_6H_6)_{0.5}$ in 10 ml of dry dichloromethane, a solution of 0.04 mmol of ligand in 10 ml of dry dichloromethane was added at r.t. The mixture was stirred for 1.5–2 h and filtered through a syringe-tip filter (0.45 μm). After addition of 20 mmol of styrene, the solution was heated to reflux, and 2 mmol of diazoacetate in 20 ml dichloromethane was slowly added over 5 h at reflux temperature. The resulting mixture was refluxed for certain additional hours, cooked to room temperature and then passed through a silica gel plug to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel with petroleum ether/ethyl acetate (95:5) to afford 2-phenylcyclopropane carboxylate. The *cis*/*trans* ratio of ethyl 2-phenylcyclopropane car-



a R = Me **b** R = $PhCH_2$ **c** R = *i*-Pr **d** R = Ph **e** R = *t*-Bu

Scheme 1. (i) H_2O_2/HOAc, 78°C, 9 h, 83%; (ii) $PhSO_2Cl$/PhH, reflux, 2 h, 60%; (iii) NaCN, NaI/acetone, 20 h, 69%; (iv) NaH, MeI/DMSO, 9 h, 60%; (v) amino alcohol, $ZnCl_2$/PhCl, reflux, 3 days, 41–84%.

boxylate was determined by GC analysis on a 30 m capillary column (Supelco 2-4318) operated at 100°C for 5 min, then programmed at 4°C/min to 200°C [$T_R = 13.22$ min (*cis* isomer) and 15.13 min (*trans* isomer)] and the *cis*/*trans* ratio of dicyclohexylmethyl 2-phenylcyclopropane carboxylate was determined at the same column operated at 230°C constant [$T_R =$ 14.04 min (*cis* isomer) and 15.13 min (*trans* isomer)]. Enantiomeric excesses were determined, after re-esterification with (−)-menthol, by GC analysis on a 30 m capillary column (Supelco 2-4318) operated at 210°C constant [$T_R = 7.82$ and 8.04 min for the *cis* isomer, and 8.98 and 9.31 min for the *trans* isomer].

3. Results and discussion

3.1. Synthesis of pyridinyl-oxazoline ligands

The synthesis of chiral pyridinyl-oxazoline ligands **3** started from 2-picoline as shown in Scheme 1. 2-Chloromethyl pyridine (**5**) was prepared by oxidation of 2-picoline with hydrogen peroxide and chlorination with phenylsulfonyl chloride. Substitution of chloride with cyanide followed by methylation with methyl iodide gave 2-methyl-2-(2-pyridinyl)propanitrile **7**. Ligands **3** were produced by condensation of nitrile **7** with optically pure amino alcohol in the presence of one equivalent amount of anhydrous

Table 1
Copper(I)-catalyzed asymmetric cyclopropanation of styrene with diazoacetates

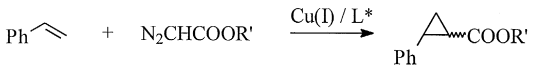
Entry	N_2CHCO_2R'	Ligand	Solvent	Yield (%)[a]	*cis*/*trans*[b]	ee% (*cis*/*trans*)[c]
1	R′ = Et	**1b** (R = Bn)	$CHCl_3$	71	31:69	23/38
2	R′ = Et	**2b** (R = Bn)	CH_2Cl_2	25	34:66	2/10
3	R′ = Et	**2b** (R = Bn)	$CHCl_3$	23	30:70	2/5
4	R′ = Et	**3b** (R = Bn)	CH_2Cl_2	66	35:65	4/18
5	R′ = Et	**3e** (R = *t* − Bu)	CH_2Cl_2	66	30:70	4/16
6	R′ = (−)-Menth	**1b** (R = Bn)	$CHCl_3$	75	23:77	55/52
7	R′ = (−)-Menth	**2b** (R = Bn)	CH_2Cl_2	33	20:80	2/15
8	R′ = (−)-Menth	**2b** (R = Bn)	$CHCl_3$	32	21:79	2/9
9	R′ = (−)-Menth	**3b** (R = Bn)	CH_2Cl_2	77	24:76	12/14
10	R′ = (−)-Menth	**3e** (R = *t* − Bu)	CH_2Cl_2	73	19:81	2/15
11	R′ = DCM[d]	**1b** (R = Bn)	CH_2Cl_2	64	14:86	47/45
12	R′ = DCM	**3b** (R = Bn)	CH_2Cl_2	92	18:82	19/14
13	R′ = DCM	**3e** (R = *t* − Bu)	CH_2Cl_2	96	13:87	11/6

[a] Isolated yield.
[b] Determined by GC analysis on a 30-m capillary column (Supelco 2-4318).
[c] Determined, after re-esterification with (−)-menthol [8], by GC analysis on a 30-m capillary column (Supelco 2-4318) at 210°C constant [$T_R = 7.82$ and 8.04 min for *cis* isomer, and 8.98 and 9.31 min for *trans* isomer].
[d] Dicyclohexylmethyl diazoacetate.

zinc chloride.[1] Introduction of two methyl groups at the methylene bridge can increase the stability of ligands in asymmetric catalysis.[2]

3.2. Copper(I)-catalyzed asymmetric cyclopropanation

Cyclopropanation reaction of styrene with different diazoacetates were carried out in CH_2Cl_2 or $CHCl_3$ by slow addition of solution of diazoacetates to a mixture of styrene and 1 mol% of chiral catalysts which were prepared in situ from copper(I) triflate and ligands (Eq. 1).



(1)

Table 1 showed the results of comparison of ligands **1–3**. Ligands **1** gave good chemical yields and moderate enantiomeric excesses in refluxing $CHCl_3$ (entries 1, 6, and 11), and there was no reaction in refluxing CH_2Cl_2. Ligands **3** have good chemical yields in refluxing CH_2Cl_2, but the enantiomeric excesses were low. Ligands **2** always provided low conversion and low enantioselectivity in either CH_2Cl_2 or $CHCl_3$ (entries 2, 3, 7, and 8). These results demonstrated that six-membered chelate ring, upon coordination, is important for heteroaryl-oxazline ligands to have high chemical yield, and both the six-membered chelate ring and the conjugation between heteroaryl ring and oxazoline unit in the ligands are necessary for enantiocontrol in copper(I)-catalyzed asymmetric cyclopropanation reaction.

[1] Catalytic amount of $ZnCl_2$ gave low yields of oxazoline products.

[2] During our studies, Fryzuk et al. [7] reported similar pyridinyl-oxazoline ligands, but no methyl groups on the methylene bridge, and their application in asymmetric hydrosilylation reaction.

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